Exhibit A

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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SMITH KLINE & FRENCH LABORATORIES LIMITED and SMITHKLINE BEECHAM CORPORATION d/b/a GLAXOSMITHKLINE,	:	Civil Action
Plaintiffs,	:	
v.	:	
TEVA PHARMACEUTICALS, USA, INC.,	:	
Defendant.	:	No. 05-197-GMS

- - -

Wilmington, Delaware
Monday, December 18, 2006
9:10 a.m.

- - -

BEFORE: HONORABLE GREGORY M. SLEET, U.S.D.C.J.

APPEARANCES:

PATRICIA SMINK ROGOWSKI, ESQ.
Connolly Bove Lodge & Hutz LLP
-and-
WILLIAM F. LEE, ESQ.,
AMY K. WIGMORE, ESQ.
MICHAEL GORDON, ESQ., and
WILLIAM G. McELWAIN, ESQ.
Wilmer, Hale LLP
(Washington, D.C.)

Counsel for Plaintiffs

A. The safety and efficacy in the ANDA process are presumed under Hatch-Waxman. We do bioequivalence to make sure we are substitutable for the brand reference product.

Q. And once an ANDA is submitted to the FDA, typically, how long does it take for the approval process?

A. FDA's average at this point is roughly 18 to 20 months.

Q. With respect to the ANDA for ropinirole, has Teva USA received the approval from the FDA at this time?

A. No. Currently, we are in the late stages of the technical review and we anticipate approval in several months.

Q. So as of today, Teva USA is not in the position to sell ropinirole. Is that correct?

A. That's true, yes.

Q. Besides the FDA approval, are there any other steps that you are aware of that need to transpire in order for Teva to be able to market ropinirole?

A. Well as a result of this litigation there is a 30-month stay that is applied to us.

Q. That 30-month stay is not yet expired?

A. Correct.

Q. Is there any other event that you are aware of that needs to transpire?

A. There is the '808 patent and the expiration of that

date.

Q. That will expire in December of 2007. Is that right?

A. Yes.

Q. So once Teva has the FDA approval, the 30-month stay expires, and December of '07 arrives, will Teva then, do you expect, be in a position to market ropinirole for the treatment of Parkinson's disease?

A. Yes, we will.

MR. ATTERIDGE: Those are all the questions I have, Your Honor.

THE COURT: Fine. Counsel.

MR. ATTERIDGE: Your Honor, I don't want to interrupt Mr. Lee's examination, but a couple of these exhibits he wants to confer are confidential and have been designated as such under the protective order. I am not sure what questions he intends to ask. But we may have an issue about wanting to have things that are confidential remain confidential. I don't know exactly who is in the courtroom with us today on these issues.

THE COURT: Perhaps the two of you would like to speak to one another.

MR. LEE: When we get to them, I could stop.

MR. ATTERIDGE: That is fine. I didn't want to interrupt without warning.

for a branded drug and the proposed trade dress for generic version?

MR. ATTRIDGE: Objection, Your Honor. There is no foundation for asking the witness who has never seen the document about its contents.

MR. LEE: I'm just asking if that is what the document appears to be because then I want to ask her if these are not the type of documents she sees in the normal course of business.

THE COURT: Why don't you ask her that.

BY MR. LEE:

Q. Do you see document you have before you?

A. Have I seen it?

Q. Yes. No. Do you see the document that refers to trade dress?

A. I don't typically see these and I don't recall this one.

Q. Fair enough. Let's look at a document that you would have seen. Turn, if you would, to tab 3.

A. (Witness complies.)

Q. Do you recognize that?

A. Yes, I do.

Q. What is tab 3?

A. This is the patent certification that was submitted in Teva's ANDA for ropinerole hydrochloride. This bears a

signature.

Q. And whose signature is that?

A. That is mine.

Q. And it's dated November 24, '04; correct?

A. Correct.

Q. Now, do you see the portion which reads, "The undersigned hereby certifies pursuant to 505J2AVII, roman numeral four, the Federal Food and Drugs and Cosmetic Act as amended, that U.S. patents 4,452,088 and 4,824,860 which have been filed for Requip tablets are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted."

Have I read that correctly.

A. Yes.

Q. Now, that certification is followed by your signature as the undersigned; correct?

A. Yes.

Q. So on behalf of Teva, you were the person certifying that the patents would be invalid, unenforceable or not infringed; correct?

A. Correct.

Q. Now, as of the time you made that certification, you had never seen the patents; correct?

A. That's correct.

Q. And you had no idea whether they were valid, enforceable or infringed; correct?

A. I'm not qualified to make that determination.

Q. Right. You relied upon Teva's lawyers to provide that information to you; correct?

A. Teva's lawyers as well as outside counsel, yes.

Q. And I'm not going to ask you about the details of their advice to you but as you told us, you are not a lawyer yourself; correct?

A. That's true.

Q. But you are responsible for insuring that the ANDA has gotten the information from all other folks you should get it from; correct?

A. Yes.

Q. And one of the things you do is rely upon your lawyers for lawyer's info; correct?

A. Yes.

Q. And having gotten that, you made your certification; correct?

A. That's correct.

Q. And in the 20 years that you have been involved in regulatory affairs, you have followed that practice of relying upon lawyers for lawyer's work; correct?

A. Yes.

Q. And you know that Teva has patents; correct?

bulb there, nerve. This would be the nigrostriatal pathway.

Q. Can you tell us then, Dr. Long, how dopamine works in connection with those parts of your body?

A. Okay. The dopamine is synthesized, stored. It's released from the nerve terminal. It crosses this synapse, a couple hundred extra. It combines in the post-junctional site and that is where the D2 receptor is. And there, it controls our motor movements.

Q. Now, there is a couple of terms you have on this slide I'd like to go through. One is there is in parentheses at the top, the pre-synaptic. Can you tell us what this mean?

A. Yes. If this is the synapse, break here in the nerve, a common term is pre-synaptic; in other words, prior to the break. And likewise, at the other end of the synapse, the lower end, this is often called post-synaptic.

Q. Dr. Long, you pointed us to a D2 receptor. Is there more than one receptor for dopamine?

A. Yes.

Q. And do they do the same thing?

A. No, they're found in different locations normally. The D1 receptor is generally associated with the smooth muscle in the kidney or mesentery artery and D2 receptor, well, central and peripherally.

Q. And do we find -- well, you mentioned the D2 receptor. What is the one we're interested in for purposes of

Q. Dr. Long, I will ask you to please turn to Tab 5 in your binder, which is DTX-160?

A. Okay.

Q. Dr. Long, do you recognize DTX-160?

A. Yes. This is a publication by Professor Cannon and myself in JM Med Chem 1978.

Q. Did you consider that article in connection with forming your opinion in this case?

A. Yes, I did.

MR. DONOVAN: I will offer DTX-160.

MR. LEE: No objection.

THE COURT: It is admitted.

(Defendant's Exhibit No. 160 received in evidence.)

BY MR. DONOVAN:

Q. Let's stay on the first page here, Dr. Long. Dr. Long, what was the date of publication of this article?

A. This was 1978. I don't know the months.

Q. '78 is good enough.

A. All right.

Q. You are one of the co-authors on this article?

A. Yes.

Q. Now, did this article relate to your research on D-2 agonists?

A. Yes, it does.

Q. Was there any dopamine agonists that you tested that are described in this article?

A. Yes. Derivatives of dopamine that we prepared and tested.

Q. Could we please turn to those dopamine receptors you tested?

A. Okay. That is on the next page, 249. Can we highlight the structures, about the middle of the left-hand column.

Okay. Up at the top, notice that this is the structure of dopamine that we were talking about before. If we have R equals H, in other words, NH-2, that would be dopamine. So what we did then was to place on that nitrogen then dimethyl groups, diethyl groups, that's No. 2, C-2H-5, dipropyl groups, C-3H-7, and dibutyl groups, C-4H-9.

Q. Dr. Long, did you test any of those compounds to see if they were dopamine agonists?

A. Yes.

Q. Were any of them dopamine agonists?

A. Yes. Compound 2 and Compound 3 were D-2 receptor agonists.

Q. Can you show us the tests you did to show dopamine receptors D-2 agonist activity?

A. Table I. This is the test results here from the cardioaccelerator nerve stimulation rate, which was my

A. Okay. Claim 3 was a method for treatment of Parkinson's disease with ropinirole. Claim 1 involves the chemistry of the chemicals in this patent.

Q. Claim 1, does that cover more than one compound for treating Parkinson's disease?

A. Yes, I didn't add them up. But there must be 15 or 20 there.

Q. Did you consider Claim 1 in connection with forming your opinions in this case?

A. Yes.

Q. Did you form any opinion about Claim 1?

A. Yes. There is compounds there that I wouldn't expect activity with.

Q. What do you mean you wouldn't expect activity with?

A. No activity at D-2 receptors, centrally or peripherally.

Q. What if anything would that relate to a method of treating Parkinson's disease?

A. Well, if they are inactive with D-2 receptors, they would be inactive for therapy with Parkinson's disease.

Q. Dr. Long, can you point us to substitutions that you believe would render the claim, render the compound inactive?

A. I don't know whether I can point you. I might have to discuss it. I am having trouble with pointers.

here instead of 1 to 4, which is what is in the '860 patent.

Q. Just so His Honor is clear, what you have just done for us is compare the genus claim of the '808 patent is 1 through 6. Correct?

A. Right.

Q. With the genus claim of the '860 patent, which is 1 to 4. Correct?

A. Right.

Q. So the genus claim of the '860 is narrower than the genus claim of the '808. Correct?

A. I don't know what genus means. I think so.

Q. Well, the group. The group --

A. Yes. The alkyl substitutions, yes.

Q. Dr. Long, you will have to let me finish, then I will let you finish. Otherwise, we will kill the court reporters.

A. All right.

Q. Dr. Long, the group that claims 1 to 4 is narrower than the group that claims 1 to 6. Correct?

A. Correct.

Q. The one that claims 1 to 4 is the '860 patent. Correct?

A. Well, 1 to 4 would also be included in the '808 patent.

Q. But the narrower claimed group is the '860 patent.

Correct?

A. Yes.

Q. Now, the '808 patent, which has the broader group -- correct?

A. Yes.

Q. You are not challenging that genus, are you?

A. No.

Q. So you are not challenging the broader one, just the narrower one. Correct?

A. Correct.

Q. Now, as background, you mentioned on a number of occasions Dr. Cannon. Correct?

A. Yes.

Q. He is sitting here in the courtroom. Correct?

A. Yes.

Q. He is a colleague of yours, as you said?

A. Yes.

Q. He has been a good friend of yours for decades. Correct?

A. Yes.

Q. You began working together in 1963?

A. Shortly thereafter, yes.

Q. You have authored several articles together?

A. Yes. Many.

Q. And I think, as you mentioned, Dr. Cannon is a

1,000. The one thing we can agree upon is none of them ever published on ropinerole before May 21st, 1987; correct?

A. Probably true.

Q. As far as you know, not one of them synthesized ropinerole before May 21st, 1987; correct?

A. As far as I know.

Q. As far as you know, not one of them ever suggested that ropinerole could be used for the treatment of Parkinson's disease; correct?

A. As far as I know, yes.

Q. And as far as you know, all of them had access to the public information you talked about with Mr. Donovan today; correct?

A. I presume so.

Q. And not one of them made ropinerole, tested ropinerole or suggested that ropinerole would be useful in treating Parkinson's disease; is that right, sir?

A. As far as I know.

Q. Now, let's go to the structure activity relationship question. We talked about a little bit before; correct?

A. Correct.

Q. Now, you would agree with me, or maybe you won't. Let me ask it to you this way. Do the structure activity relationships with respect to one series of compounds necessarily translate to another series of compounds?

A. Not necessarily. And a beautiful example would be structure activity relationships in apomorphine and dissection products vs., say, the structure activity relationship in the ergots. They're very different.

Q. Sure. Now, one of the reasons we know that is because you tested both; correct?

A. Yes, you have to have the data to form a hypothesis.

Q. Right. Now, you tested indoles; correct?

A. Yes.

Q. But you never tested indolones; correct?

A. Correct.

Q. So you never had the data to draw the hypothesis on the structure activity relationship between those two series of compounds; correct?

A. We've never written in the area, no.

Q. But you did write what was introduced today as DTX-179. It's in tab 7 of the only notebook I think you have before you now.

A. Okay. I beg your pardon. What number?

Q. It's tab 7.

A. Okay.

Q. And I think probably Dr. Long, the easiest way for me to refer to it, this is the 1986 Cannon article.

A. Wait a minute. Did you say, I'm sorry, tab 7?

Q. Tab 7.

Q. Now, the publication addresses the design of potential drugs; correct?

A. Yes.

Q. And specifically, it discusses the design of potential anti-Parkinsonian drugs; correct?

A. Yes.

Q. And in fact, it describes some work that you did with Dr. Cannon; correct?

A. Yes.

Q. Now, turn, if you would, to page 173.

A. (Witness complies.)

Q. Now, Mr. Donovan asked you about some portions of this article and the conclusions that one of ordinary skill in the art would have drawn from this article. Do you remember that?

A. Yes.

Q. All right. And you told him what your view was. I want to ask you about some other portions of the same article.

A. Okay.

MR. LEE: And I'm going to ask you to have blown up so it's easier to read the sentence, the bottom of the right-hand column that begins, "thus, within a given."

BY MR. LEE:

Q. Now, I want to take us through this and the portion

that goes on to the next, to the bottom of the page. Let's start with the sentence that says: Thus, within a given chemical series of agonists, there may be a well defined structure activity and stereochemical correlation.

Have I read that correctly?

A. Yes.

Q. An indole is a chemical series of agonists; correct?

A. That's correct.

Q. An indolone is a different chemical series of agonists; correct?

A. This wasn't written comparing with indolones or anything like that, I'm sure.

Q. I understand. Because you never did that?

A. Yes.

Q. The next sentence: But these correlations may disappear when a different chemical series of agonists is addressed, and a new combination of structural parameters and stereochemical requirements may apply.

Have I read that correctly?

A. Yes.

Q. Now, you agree, do you not, that that was an accurate statement of the state of the field in 1986?

A. I agree. And it is accurate.

Q. Let's go on to the next sentence. Well, let me ask you this: So you agree that if you make a finding with

respect to the structure activity relationship of one series, you don't know that is going to translate to another chemical series; correct?

A. It's correct, and it's a matter of expectation here. If you go from a dissection product in say one series, say apomorphine, and you go to another series and out of apomorphine you would have expectations there, but what I think he is writing about here is going from apomorphine type compounds over to the ergots and there you have all kind of chiral centers and on and on which I'm not acquainted with.

Q. And when you go from one series to another, you would form a hypothesis and then expect nothing; correct?

A. I don't agree.

Q. Well, let's see what you said in your deposition.

A. Okay.

MR. LEE: Page 70, line 13.

Page 70. I'm sorry. Page 70, line 13.

BY MR. LEE:

Q. "Question: So you don't know if you make a finding with respect to one series if that's going to translate to another chemical series; is that correct?

"Answer: No, that -- yes, no, you would certainly incorporate it into your hypothesis and expect nothing."

A. Yes.

Q. That was your testimony; correct?

A. I think so. Yes, the testimony is correct.

Q. Sure. And it was true at the time; correct?

A. Yes.

Q. And it's true today; correct?

A. Yes.

Q. Now, we go back to the article and the portion we were looking at.

The last sentence says:

"If this be true, structural comparisons and correlations between ergoline derivatives, apomorphine derivatives and other dopaminergic agonist molecular systems may not only be meaningless, but actually may be misleading."

Have I read that correctly?

A. You sure did.

Q. Now, let me focus on the "if this be true." Do you see that portion?

A. Yes.

Q. That is referring back to the two sentences that you and I just read; correct?

A. I think so.

Q. And we agree it is in fact true?

A. Yes.

receptors at all; correct?

A. No, that isn't correct. They go back to mid 60s. Leon Goldberg proposed the cardiovascular dopamine receptors as D2.

Q. But the first time anybody proposed that two receptor model was in 1979; correct?

A. Yes.

Q. All right. Now --

A. But this is their model. Yes.

Q. Sure. Now, it was understood by at least the early 1980s that there were different types of receptors; correct?

A. Correct.

Q. And the literature in the early 1980s described numerous dopamine receptors subtypes; correct?

A. Correct.

Q. And you would agree with me that the evidence of classification of those subtypes was not always very convincing; correct?

A. Well, it depends which two or which ones you are talking about. For example, the D3, D4, D5 certainly is not. You know, they're primarily biochemical markers. The D1, D2 has been well recognized for many years.

Q. Well, let me ask you this. Can you tell us whether you would agree with this statement? Evidence of classification is not always convincing and correlation

central mechanisms?"

Have I read that correctly?

A. Yes.

Q. So what you were comparing is the effect of compounds on the peripheral mechanism and the effect of compounds, the same compounds on the central mechanism?

A. Yes.

Q. And you would agree with me that by 1978, when a scientist working in the field wanted to identify the central system, they knew how to do it; correct?

A. Oh, yes. Yes.

Q. When they wanted to identify the peripheral system, they knew how to do it; correct?

A. Yes.

Q. And when they wanted to distinguish between the two, they knew how to do it; correct?

A. Yes.

Q. In fact in the '860 patent, Dr. Owen is very clear in identifying the effects on this peripheral nervous system; correct?

A. And also the '808 patent, too.

Q. Right. But never identifies effects on the central nervous system by name, do they?

A. Not in the patent, no.

Q. Right. Now, did you think they didn't know how to

Q. And in 1987, one of ordinary skill in the art would have understood that the requirements for peripheral and central dopamine receptor stimulation may differ; correct?

A. Well, yes. And I think we showed that. And we showed it in this article. If you will read it carefully.

Q. Fair enough. Now, there are some compounds that act at the peripheral D2 receptor but don't act at the central D2 receptor; correct?

A. There are known, yes.

Q. And you knew of that in 1986; correct?

A. Some time. I don't remember when.

Q. Well, would one of ordinary skill in the art have known in 1987 that there are some compound that act at the peripheral D2 receptor but not at the central receptor?

A. Oh, yes.

Q. Now, Dr. Long, yesterday you gave His Honor your opinion that if you knew something was active at the peripheral D2 receptor, you would know or expect it to be active at the central D2 receptor. Do you remember that?

A. May I correct or add a little here? What I think I testified was that you would expect a peripherally D2 dopamine agonist to react at the receptor site. That does not mean it occurs 100 percent of the time and if I gave that impression, I'm sorry.

Q. I didn't mean to suggest you did but let's take your

Q. There is the 1985 publication. Correct?

A. Correct.

Q. We are going to come to that in a few minutes. Is it your testimony that Mr. Gallagher reported a finding that ropinirole crossed the blood brain barrier?

A. It would be the interpretation a pharmacologist would have.

Q. I will try to be more precise.

A. There is no steady assay of the compound after it's crossed. This is inference. It's expectation.

Q. So if we compare what was known about ropinirole with what was needed for Parkinson's, what was known was that ropinirole was pre-synaptic but for Parkinson's you wanted post-synaptic; correct?

A. Correct.

Q. It was known that it was active in the peripheral nervous system but for Parkinson's, you want it to be active in the central nervous system; correct?

A. Correct.

Q. You knew that it had to cross the blood brain barrier to be active in the central for Parkinson's; correct?

A. Correct.

Q. And no one had reported that finding; correct?

A. By inference on the decrease in locomotion because dopamine receptor agonist decreased locomotion in rodents in

"central" to describe the central nervous system and how to use the word "peripheral" to describe the peripheral nervous system; correct?

A. Yes.

Q. Now, it's true, is it not, that Parkinson's disease is not mentioned by name anywhere in the '808 patent; correct?

A. Correct.

Q. Turn, if you would, in column four to lines 31 to 34.

A. Okay.

Q. "More specifically, the compounds of this invention, especially, 4-(2-di-n-propyl-amino-ethyl)-2-(3H) indolone hydrochloride, have proved to be selective peripheral D2 agonists."

Have I read that correctly?

A. Yes.

Q. The compound is ropinirole hydrochloride; correct?

A. Correct.

Q. It is selective for a peripheral D2 agonist; correct?

A. Correct.

Q. At no point does the patent state that ropinirole hydrochloride is selected for a central D2 agonist; correct?

A. Correct.

Q. At no point does the patent state that ropinirole crosses the blood brain barrier; correct?

A. Except indirectly as discussed easier.

Let me ask you a different question. As of the time, as of May 1987, was confusion sky-high, to use your words, about the alpha and beta-D2 dopaminergic receptors?

A. It was getting, it was more in the seventies when the confusion was reigning.

Q. But did the alpha-dopaminergic receptors refer to peripheral nervous system receptors?

A. That's correct.

Q. So in this paragraph, what Mr. Gallagher is saying is, I have presynaptic peripheral D2 receptors. Correct?

A. Correct.

Q. The term post-synaptic never appears anywhere in the patent. Correct?

A. Correct.

Q. Now, in the next paragraph at Column 4, Line 45, there is a discussion of the perfused ear artery test. Do you remember that?

A. Yes.

Q. That is the part that you said in part would lead someone to believe that ropinirole hydrochloride would be selected for the post-synaptic central D2 receptor. Correct?

A. Correct.

Q. Now, Dr. Long, by 1987, those of ordinary skill in the art knew that the rabbit ear artery test was a test for

peripheral D2 activity, didn't they?

A. Yes.

Q. You cited a 1978 article to His Honor yesterday. Do you remember that?

A. Yes.

Q. But a lot happened between 1978 and 1987 in this field, didn't it?

A. Not with the rabbit ear artery. That continued.

Q. By 1987, the rabbit ear artery test was a test for the peripheral nervous system. Correct?

A. Correct.

Q. Now, let's --

MR. LEE: If I may approach, Your Honor?

THE COURT: You may approach.

BY MR. LEE:

Q. I am going to give you DTX-172. This is a 1978 article. Right?

A. Yes.

Q. This is an article you told His Honor yesterday that you read and a light bulb went off in your head. Correct?

A. Yes.

Q. I want to make sure --

MR. LEE: This is in the blue binder, Your Honor.

THE COURT: I have it.

Q. It was published in 1981. Correct?

A. Correct.

Q. Let me draw your attention to Page 1116.

A. Okay.

Q. Now, do you see the Structure 10 at the top of Column 2?

A. Yes.

Q. That compound is aminotetralin. Correct?

A. Yes.

Q. And you found that it was a pre-synaptic peripheral dopamine agonist; correct?

A. Correct.

Q. And a pre-synaptic peripheral dopamine agonist like that reported by Mr. Gallagher in the '808 patent; correct?

A. Yes.

Q. But that same compound had little effect on the post-synaptic dopamine receptors in the brain; correct?

A. Correct.

Q. And, in fact, you so reported at page 1116; correct?

A. Yes.

Q. So you knew and, in fact, had reported to the scientific community as of 1981 that there were compounds that were active pre-synaptically in the periphery but were not active post-synaptically in the central nervous system; correct?

A. Yes, there were a few in this category.

Q. And you had to test them to find out?

A. Right.

Q. Now, yesterday, I asked you about whether a compound nine had ever made it to the clinic. Do you remember that?

A. Yes.

Q. And you testified that it hadn't?

A. I was probably wrong. I don't know. Are you referring to the Cassidy patent?

Q. Yes. Well, I was going to ask you. Your testimony was there was a patent issued on it. Do you remember that testimony yesterday?

A. I found that out a day or two ago.

Q. Yes. And, in fact, that is a patent called the Cassidy patent; correct?

MR. DONOVAN: Objection, Your Honor. As Dr. Long said, this was just faxed to us literally over the weekend. We have an agreement we're not going to use any exhibits for any purpose other than impeachment without good cause shown. This exhibit was faxed to us over the weekend for the first time. We'd say it's not properly being used here at this time.

MR. LEE: Well, Your Honor, I'll use it for impeachment purposes then.

MR. DONOVAN: Your Honor, he can't use it for

Q. Dr. Long, let me ask you some questions about bromocriptine?

A. Yes.

Q. Can you turn in the notebook to the '860 patent? Do you have that?

A. Which one?

Q. Let's see what color notebook you have.

A. Black. Oh, I'm sorry.

Q. Do you have the '860 patent before you?

A. Yes.

Q. Now, let me turn your attention to column one, paragraph four, beginning at line 36.

A. All right.

Q. "An alternative form of therapy is to administer post-synaptic dopamine agonists, for example, ergot alkaloids such as bromocriptine -- however, this approach is also associated with side effects. For example, patients receiving bromocriptine often experience dyskinesia, psychiatric problems and, in a small number of cases, experience vasospastic phenomena and angina. In addition, bromocriptine also causes psychiatric side effects such as hallucinations."

Have I read that correctly?

A. Yes.

Q. Now, bromocriptine is in fact a post-synaptic dopamine

agonist; correct?

A. At the D2 receptor, yes.

Q. And it was known in 1987 and in May of 1988 that post-synaptic dopamine agonists could be used to treat Parkinson's disease; correct?

A. Right.

Q. This sentence says that bromocriptine acts post-synaptically; correct?

A. Yes.

Q. And then the rest of the --that's true, it does act post-synaptically?

A. Yes.

Q. And you agree with me?

A. Oh, yes, 100 percent.

Q. The rest the paragraph describes side effects associated with bromocriptine?

A. Yes.

Q. Now, you agree there are side effects associated with bromocriptine?

A. Yes.

Q. And the reason there are side effects is bromocriptine is not a particularly clean compound, is it?

A. That's correct.

Q. And it can bind with a lot of different receptor sites; correct?

A. Correct.

Q. And because it can bind with a lot of different receptor sites, you can get these side effects; correct?

A. Yes, I presume so. Yes.

Q. And one of ordinary skill in the art would have known in 1987 that bromocriptine was not a clean compound; correct?

A. Yes. May I comment a moment here?

Q. Well, Dr. Long --

A. They would have known it was a nonclean compound.

Q. Okay. And would have known, the fact that it was not a clean compound would lead to the possibility of side effects; correct?

A. Correct.

Q. So the statement in the patent that bromocriptine is post-synaptic and leads to what could be severe side effects was true; correct?

A. Correct.

Q. Now, let's go to the next paragraph beginning at line 45, if we could.

"In view of the foregoing, it is clear that there is a continuing need for the provision of effective safe medicaments for the treatment of Parkinsonism."

Have I read that correctly?

A. Yes.

Q. And do you see the portion of this article at the very top of the page?

A number of different chemical structures have demonstrated preferential agonist activity at peripheral pre-junctional D2, vis-a-vis, post-junctional D1 receptors.

Have I read that correctly?

A. Yes.

Q. And the next sentence identifies bromocriptine as one of the examples, many examples of these compounds; correct?

A. Correct.

Q. Now, the article is talking only about post-junctional D1 receptors; correct?

A. Well, that's what it says.

Q. Right. And when you testified to His Honor about this yesterday, we didn't look at the first portion of the article that tells us what they're preparing. They're comparing the peripheral pre-junctional D2 with the post-junctional D1; correct?

A. That's what they say.

Q. Right. And there is nothing in the article that says bromocriptine is not post-synaptic; correct?

A. Right.

Q. All right. Now, turn, if you would, back to the '860 patent.

A. Eight?

Q. '860 patent.

A. And that was tab?

Q. Try tab 6.

A. Okay. I've got it.

Q. Got it?

A. Yes.

Q. And I want to take you to Claim 1 of the '860 patent that you testified about yesterday.

A. Okay.

Q. Do you remember that?

A. Yes.

Q. Now, you testified about whether some of the compounds within that claim would not work; correct?

A. Right.

Q. Now, you've read the patent carefully many times you've told?

A. Yes.

Q. You read the examples; correct?

A. Yes.

Q. And it's true, is it not, that one compound that is described in the patent specifically as having been subjected to tests is ropinirole hydrochloride; correct?

A. That's true.

Q. Now, in the '860 patent, would you turn to column one, lines 48 to 53?

A. (Witness complies.)

Q. Now, in that paragraph we are specifically referring to indolone derivatives. Correct?

A. Correct.

Q. And those are the indolone derivatives that are claimed in the patent. Correct?

A. Correct.

Q. And the group of compounds that is claimed in Claim 1 is a group of indolone derivatives. Correct?

A. Correct.

Q. Now, reading the patent as an expert, as you are, you knew that the one compound that had been tested was ropinirole hydrochloride. Correct?

A. Correct.

Q. There is no statement in the patent that any other compounds had been tested. Correct?

A. Correct.

Q. Now, you have some patents of your own, don't you?

A. I have some what?

Q. You have some patents of your own, don't you?

A. Yes.

Q. And you have patents that have, if I could have Claim 8 -- I am sorry, Claim 1 back up.

A. Okay.

Q. Now, this is the formula that describes a group of

compounds that you testified about yesterday. Correct?

A. Yes.

Q. And you understand as an experienced pharmacologist that what the formula tells us is the different positions R, R1, R2, R3, and you can substitute different things. Correct?

A. Correct.

Q. You have patents of your own with generic formulas just like that, don't you, sir?

A. I don't remember.

Q. Let me see if I can refresh your recollection.

A. Okay.

MR. DONOVAN: Objection, Your Honor. He is using it to refresh his recollection. I don't know if that warrants putting it up on the screen.

MR. LEE: We can take it off the screen.

MR. DONOVAN: Fair enough.

BY MR. LEE:

Q. Dr. Long, you recognize this patent, the '063 patent?

A. Yes.

Q. Does it refresh your recollection that you, yourself, have patents claiming genuses of compounds?

A. What?

Q. Let me do it in a non-lawyer way. Does it refresh your recollection that you, in fact, hold patents that have

in the claims groups of compounds?

A. Well, yes, but I am really not acquainted with -- Dr. Cannon took care of all of the patent aspects, what little we had.

Q. So what you did -- would you like some water?

A. Yes.

Q. You do have several patents issued in your name. Correct?

A. Right.

Q. What you did is you did the scientific work. Correct?

A. The pharmacology.

Q. Dr. Cannon did the chemistry. Correct?

A. Yes.

Q. It then went to patent lawyers or patent agents working with the University of Iowa. Correct?

A. Yes.

Q. And you relied upon --

A. I think so. I really don't know. I presume so.

Q. As far as you know?

A. Yes.

Q. And you relied upon them to do their job. Correct?

A. I think so.

Q. And in terms of defining the claims that would actually be submitted to the Patent Office, you relied upon them. Correct?

A. I didn't really, no. Dr. Cannon took care of this.

Q. So you have, on the patents on which you are a named inventor, you have no idea how the specific claims came to be. Correct?

A. That's right. I didn't write these.

Q. You relied upon Dr. Cannon and you relied upon --

A. Yes.

Q. -- and you relied upon the lawyers working for you to do their job. Correct?

A. Whoever did it. I don't know whether these were universities or consultants.

Q. But you relied upon them to do their job?

A. I may not have even known Dr. Cannon filed it. I don't know.

Q. Lastly, you understand that the attack on Claim 1 is a charge that it was obtained by inequitable conduct. You know that. Correct?

A. No, I didn't know that.

Q. No one has asked you to review the records to see if there is any evidence of an intent by anyone associated with Dr. Owen or GSK to defraud the Patent Office. Correct?

A. No.

Q. Is that correct?

A. Correct.

MR. LEE: Nothing further, Your Honor.

susceptibility of Compound 9, where the hydroxyl group is introduced at the 6 position, one of the positions which is chemically susceptible to oxidative attack, to the extent that we would have any expectation about whether it is less electron-rich and therefore more difficulty to oxidize indolone should be attacked, you would have an expectation that it would not occur at the 6 position. It would occur somewhere else. Therefore, it reduces -- well...

Q. Do you have any idea, yourself -- propenyl is in fact metabolized?

A. I don't know specifically, no.

Q. If it were to be metabolized it would be metabolized at a different position?

A. That is what we would expect.

MR. DONOVAN: Objection, misleading.

THE COURT: Misleading, counsel.

BY MR. McELWAIN:

Q. I would like to have you turn to the genus claims of the '860 patent. As part of your work in this case, have you considered the reasonableness of the scope of those claims?

A. Yes, I have.

Q. And have you formed an opinion as to whether their scope is reasonable?

A. Yes, I have.

Q. What is your opinion?

A. They are quite reasonable.

Q. And what is the basis of that opinion?

A. The basis of that opinion is comparing the genus claims of -- genus claim of the '860 patent with what was understood, and I would say the scope related to indolones in the art at that time.

Q. And what were the genus claims that you looked at in the prior art?

A. Well, the specific prior art that relates to two indolones were the '944 patent and the '808 patent.

Q. Could you look at Tab 10, which is PTX-36. What is Tab 10?

A. Tab 10 is the '944 patent.

Q. And I offer PTX-36.

MR. McELWAIN: No objection.

THE COURT: It is admitted.

(Plaintiffs' Exhibit No. 36 received in evidence.)

Q. What does the '944 patent disclose?

A. The '944 patent discloses, relative to the structures that we have been talking about, it discloses substituted two indolones where the substituents are at the 4 position, those being amino alkyl side chain, what we have been seeing as the top of the molecule, and also substituent at the 7

THE WITNESS: Each column represents the genus claim, and each row is an attempt to correlate variation or a substituent position with its counterpart between the three patents.

BY MR. McELWAIN:

Q. Can you summarize in general the relationship of the scope of the genus of the '860 patent to the genuses of the earlier patents?

A. I think we will find quite straightforwardly from looking at this graphic that the genus claim of the '860 patent is both much narrower than the genus claims, than the genuses claimed by the '944 and the '808 patent. There is no additional variability from the prior art patents. And in fact, within the variations permitted, they are much narrower in scope and also much narrower in character, I would say.

Q. Focusing on the first set of rows, R and R2, can you explain in general how that scope is narrower than the earlier patents and what type of substituent those are?

A. Okay. So the R for the '944 and '808 patent are defined in the same way, the R substituent on the side chain. The '860 patent is defined as an NR2, so I have listed out now what the NR2s could be based on the R definitions. For example, an R in the '860 patent is hydrogen and both of those are hydrogen and that's an

unsubstituted amino grouped.

That is permitted in both the '944 and the '808 patents. The R's in the '860 patent are limited to C1 to C4 alkyl.

So in one of those R's is C1 to C4 alkyl. That would correspond to lower alkyl amino in the '944 or C1 to C6 lower alkyl amino in the '808 patent.

That is narrower because it's limited to four atoms in the '860, whereas it is permitted up to six atoms in the '808.

Similarly, when both R's are C1 to C4 lower alkyl amino, that corresponds to dilower alkylamine, and Di-C1-C6 lower alomine in the '808' patent. That is the range of variation permitted in the side chain amino group in the '860 patent. Broader ranges are embraced I would say by the '944 patent and in the '808 patent in terms of different kinds of side chains than simple alkyl groups.

Q. What is an alkyl?

A. An alkyl group is about the simplest molecular fragment, simplest class of molecular fragments in organic chemistry.

Q. Have you prepared a slide to illustrate alkyl groups?

A. Yes, I have.

Q. If you could turn to Tab 12, PTX-28?

THE COURT: Let's take a break. I am going to

interrupt.

(Recess taken.)

BY MR. McELWAIN:

Q. Dr. Bartlett, I think we were looking at slide, PDX-28, which is tab 12. Can you explain to the Court what this slide shows?

A. Yes. And at the risk of teaching Your Honor more than you know or more than you want to know, cut me off if you want, chemists talk a lot about substituents and chemists think about substituents as attached to a molecular framework or a scaffold so we obviously have used that term a lot. I want to make it clear what I'm referring to.

I also would like to point out chemical properties are largely dependent on what chemists refer to it as functional groups. Functional groups are typically substituents which contain atoms other than just carbon and hydrogen: oxygens, nitrogens, what we call halogens and then different ways in which those things are bonded to each other.

An example of, in fact, probably the only example of substituents which are not functional groups are the alkyl groups. Those are just comprised of carbons and hydrogens and single bond and listed here the simple ones, starting from the smallest methyl all the way up to ethyl, propyl, butyl, et cetera. Those would be the alkyl groups.

Q. Would it help to take a look at the DeMarinis article?

MR. DONOVAN: Yes.

MR. McELWAIN: That's DTX-319, which is tab 14.

MR. DONOVAN: Your Honor, I have no objection to the DeMarinis article, which is already in evidence.

I do have an objection to this line of testimony. It's not in his report as to how he is distinguishing Dr. Cannon's or, excuse me, Dr. Long's testimony.

MR. McELWAIN: Paragraph 76 of the report.

THE COURT: Would you identify?

MR. McELWAIN: Paragraph 76.

THE COURT: Mr. Donovan, have you reviewed paragraph 76 of the report?

MR. DONOVAN: Your Honor, I'll withdraw my objection.

THE COURT: Okay.

BY MR. McELWAIN:

Q. In tab 14, DTX-319 we have on the screen. And is there a portion of the document which you should be looking at now?

A. If we turn to page 943, table 4.

Q. And what does this table show?

A. Well, this table is purporting, as table indicates, the agonist activity of some of the substituted indolones at

a pre-junctional dopamine receptor. And if I didn't know it before, I certainly know it now, that this particular assay is, well, does say below, an isolated perfused rabbit ear artery, so I understand that to be a peripheral assay.

It lists the EC 50, so it will be an effective concentration for 50 percent of the response, as it says here, down below, the table, for a variety of compounds. And to make sure we understand what an EC 50 refers to, it refers to a concentration that is required to produce an effect. The larger the number, the less active the compound.

And we see a wide range of activities for compounds here. Compound 31, as pointed out, has only a lower limit for any potential activity that might be present. It says it's greater than 3,000. That says to me that that compound -- first of all, that says to me, and I would believe one of ordinary skill, that compound is no longer interesting from the perspective of one of skill in the art who is looking for better compounds.

But I also note that there is compound on this which are listed at a compound and this is listed as even having a lower activity; a higher threshold, as it were. Compound 47 is indicated as having an EC 50 which is greater than 10,000 nanomolar or 10 micromolar. There are a couple things I guess I would point out.

One I would infer from this comparison that there is relative, between 31 and 37, that 31 must somehow show more suggestion of activity than compound 47 does. And I would also observe that in general, inactivity of three or five or ten micromolar is not inactive in an absolute sense.

Q. Now, were you also here when Dr. Long testified about the purported lack of activity of certain dibutyl forms of dopamine?

A. Yes.

Q. Could we turn to tab 15 of the binder? This is DDX-10.

BY MR. McELWAIN:

Q. What does this demonstrative show? Again, Defendant's Demonstrative.

A. Again, this is a demonstrative which Dr. Long used and designated this compound as inactive. I don't believe that has been proven in any sense.

Q. And why do you disagree?

A. Well, I'm not aware of any testing of this compound in any assay, peripheral or central. And my understanding is that the only assays in which, the only experiments in which an N-dibutyl compound has been demonstrated to be inactive or have low activity was in a completely different chemical series than an indolone.

Q. What was that chemical series?

A. That chemical series was in the catechol series.

MR. McELWAIN: I have no further questions, Your Honor.

I believe I may not have offered demonstratives PDX-22 and 25.

MR. DONOVAN: Do you have the tab?

MR. McELWAIN: It's tab 5 and tab 8.

MR. DONOVAN: Subject to our sidebar, I have no objection to the demonstrative.

THE COURT: The exhibits are admitted.

* * * (Plaintiffs' Demonstrative Exhibit Nos. 22 and 25 were received into evidence.)

MR. McELWAIN: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. DONOVAN:

Q. Good afternoon, Dr. Bartlett.

A. Good afternoon, Mr. Donovan.

Q. You provided us some testimony about the reasonableness of Claim 1 of the '860 patent?

A. Yes.

Q. In fact, you used the term "genus" in your testimony?

A. I believe I did.

Q. Now, you're not a lawyer?

A. No.

Q. And you're not offering any legal opinions; right?

from two earlier GSK patents. Do I have that right?

A. I think that all of the compounds which are encompassed in the genus of the '860 patent would be found in either the '944 or the '808.

Q. And on that basis, you believe they are reasonable; correct?

A. In light of the prior art.

Q. Now, one of the GSK patents that you find these compounds in is the '944 patent; correct?

A. Yes.

MR. DONOVAN: And if we could pull up the '944 patent?

BY MR. DONOVAN:

Q. This is the '944 patent that some of the compounds in Claim 1 of the '860 have?

A. Yes.

MR. DONOVAN: And if we could go to the first column of the '944 patent.

BY MR. DONOVAN:

Q. And under the description of the invention, there is a description of the various compounds that are disclosed in this '944 patent; right?

A. Yes.

Q. Do I have it right there?

A. Yes. I think I misspoke when I answered that all the

compounds in '860 could be found individually either in the '944 or '808. I think there is a combination of substituents which individually would be found in one of the other patents, not being combined until the '860.

Q. Sort of a mix and match?

A. Yes.

Q. Now, this '944 patent describes a number of different compounds also using a generic formula with a substitution; correct?

A. That's true.

Q. And you reviewed this patent; correct?

A. Yes.

Q. Now, you don't know from this patent, Dr. Bartlett, whether any of these compounds are dopamine agonists; true?

A. Well, they are put forth in the '944 patent as an invention of the inventors, as a discovery of the inventors having that activity. So whether the activity is explicitly described in the patent in terms of an example or whether it is disclosed in the patent by virtue of the claims, I think one of skill in the art understands that these compounds as a genus would have that activity.

Q. Well, you couldn't tell from the '944 patent whether the '944 patent disclosed whether these compounds were dopaminergically active, correct? That is more of a pharmacology opinion, isn't it?

isn't it?

A. That corresponds to Compound 31 of the DeMerinis article.

Q. And what GSK says in this paper is that that Compound 31 of the DeMerinis paper was found to be inactive. Correct?

A. It says that it was inactive in what I understand to be a peripheral, an assay for peripheral activity. And I think you will have to ask somebody with more pharmacology background as to whether that proves that it's inactive for an application which would require central activity.

Q. What the article says, Dr. Bartlett, is that that compound was, quote, inactive. Correct?

A. It says that it was inactive for inhibition of vasoconstricture caused by electrical stimulation of the rabbit ear artery. I understand that that is a peripheral assay.

MR. DONOVAN: I would offer DTX-376.

MR. McELWAIN: No objection.

THE COURT: It is admitted.

(Defendant's Exhibit No. 376 received in evidence.)

THE COURT: Redirect.

MR. McELWAIN: No questions, Your Honor.

THE COURT: Thank you, Dr. Bartlett.

A. Yes.

Q. What are those?

A. These are representations of storage vesicles in which dopamine is concentrated and it's when the electrical impulses pass down the nerve cell, it then stimulates these vesicles to release dopamine into the synaptic cleft.

Q. And what are the blue shaded dots on this diagram?

A. These blue things are dopamine modules.

Q. Now, what is a dopamine receptor?

A. A dopamine receptor is a protein embedded in a nerve cell membrane that recognizes dopamine and as a result of that recognition causes biochemical change to occur and then the generation of electrical impulse.

Q. Are there receptors identified on this diagram?

A. There are.

Q. Where are they?

A. We have receptors both located post-synaptically so they're on the dendrite or cell body of the next nerve cell in the chain. And we have receptors which are indicated as being pre-synaptic, and that is located on the terminals of the nerve from which dopamine is being released.

Q. And in terms of dopamine receptors generally, are there different subtypes?

A. Oh, yes. This time, we believe there are D1, D2, D3, D4, and D5 dopamine receptors.

Q. And when are those different types of dopamine receptors discovered?

A. Well, the first description of multiple dopamine receptors was in 1979 by Kebabian and Kahn. And subsequently during the 1980s, we had a period of immense change, a very exciting era but an era in which there was terrible confusion and chaos over the way in which dopamine receptors should be classified.

Q. Now, you mentioned D1 receptors. Where are they located?

A. D1 receptors are both in the peripheral nervous system and in the central nervous system.

Q. And where are D2 receptors located?

A. D2 receptors are in both peripheral nervous system and the central nervous system.

THE COURT: I think you might have turned it off.

THE WITNESS: Maybe the battery is running out. How am I doing?

THE COURT: She has another one.

THE WITNESS: There we go. Thank you very much.

(Portable microphones are switched.)

THE WITNESS: Okay.

Oop. Sorry. It frightened me that time.

(Laughter.)

Q. Now, what is a dopamine agonist?

A. A dopamine agonist is a molecule which will interact with a dopamine receptor so as to mimic the effects of dopamine agonist itself.

Q. Are there different sites within the body that a dopamine agonist can act on?

A. Well, a dopamine agonist can act in the peripheral nervous system or in the central nervous system. It can act on pre-synaptic receptors. It can act on post-synaptic receptors.

Q. Are dopamine agonists used to treat Parkinson's disease?

A. They are.

Q. And is there a particular site that a dopamine agonist needs to act on to treat Parkinson's disease?

A. Yes. A dopamine agonist needs to act on a post-synaptic dopamine receptor in the right area of the central nervous system to have a beneficial effect in Parkinson's disease.

Q. Can you just point to us where on the diagram that is?

A. This would be here. This would be these receptors in the post-synaptic side of this synapse.

Q. Professor Jenner, can dopamine itself be administered as a drug to a patient suffering from Parkinson's disease?

A. No.

A. I did.

Q. And would your opinion on the '860 patent change in any way if the definition offered by Dr. Long was accepted?

A. No.

Q. I would like to now turn your attention to what is Tab 2 in your binder, which is PTX-13. It has already been admitted. Do you recognize this document, Professor Jenner?

A. Yes. This is the '808 patent.

Q. And have you reviewed this patent in evaluating whether Claim 3 of the '860 patent was obvious?

A. I have.

Q. And have you formed an opinion as to whether Claim 3 of the '860 patent would have been obvious in light of this patent, the '808 patent alone?

A. My opinion was that the '860 patent Claim 3 would not have been obvious in light of the '808 patent.

Q. And why not?

A. Because this is a patent that deals with peripheral dopamine receptors and it does not deal with drug effect at central dopamine receptors.

Q. Does this patent, the '808 patent, tell us anything about whether ropinirole hydrochloride would get into the brain?

A. No.

Q. Does the '808 patent tell us anything about whether

ropinirole hydrochloride would treat Parkinson's disease?

A. No.

Q. Is the term Parkinson's disease mentioned anywhere in the '808 patent?

A. No.

Q. I want to direction your attention to Column 4 of the '808 patent, Line 31, and specifically, I want to direct your attention to the sentence beginning on Line 31, Starting more specifically?

A. Yes.

Q. Have you read that sentence?

A. Yes.

Q. What compound is described in that sentence?

A. That's ropinirole hydrochloride.

Q. What does that statement tell one of ordinary skill in the art about the activity of ropinirole hydrochloride at D-2 receptors?

A. This would tell one of ordinary skill in the art that ropinirole hydrochloride was active on peripheral dopamine receptors.

Q. What language in that sentence indicates that?

A. Have proved to be selective peripheral D2 agonists.

Q. And in the same column, could you refer quickly to Line 38. Do you see the sentence beginning, Otherwise speaking?

A. Because if you look at this claim in the context of the whole patent, it is abundantly clear that the authors are talking about peripheral presynaptic dopamine receptors.

Q. Now, Professor Jenner, have you reviewed this patent from cover to cover?

A. I have.

Q. Have you seen any mention of Parkinson's disease in this patent?

A. No.

Q. Have you seen any mention of ropinirole acting centrally in this patent?

A. No.

Q. Have you seen any mention of ropinirole acting post-synaptically in this patent?

A. No.

Q. Now, in general, what was known about the classification of dopamine receptors at the time of the invention of the '860 patent in May of 1987?

A. Well, by this time it was largely thought that dopamine receptors fell into two major families. And that would be the D1-like receptor family and the D2-like receptor family.

Q. And as of May of 1987, what would one of ordinary skill in the art have known about the relationship of central D2 receptors and peripheral D2 receptors?

A. One of ordinary skill in the art would have thought that these receptor systems were different.

Q. And at the time of the filing of the '860 patent, if you knew a compound was a pre-synaptic D2 agonist in the periphery, could you, could one of ordinary skill have predicted whether it would be a post-synaptic D2 agonist in the central nervous system?

A. No.

Q. Why not?

A. Because, first of all, it was not clear whether D2 pre-synaptic receptors, pre-synaptic dopamine receptors in the periphery were the same or not as post-synaptic D2 receptors in the brain.

Secondly, it would not be clear that any compound concerned would be able to penetrate through the blood brain barrier to reach a post-synaptic D2 receptor in the central nervous system.

Q. As of May of 1987, were there examples of compounds that were thought to act peripherally but not centrally on dopamine receptors?

A. There were compounds which would act peripherally on dopamine receptors but not centrally.

Q. Can you give us some examples?

A. There were two compounds in particular which at this time would be viewed as fitting into that classification.

disease?

A. No.

Q. Are you familiar with the rabbit ear artery test described in this article?

A. I am.

Q. What is that used for?

A. It is an isolated tissue preparation, which is used to look locally at the effects of drugs on peripheral presynaptic dopamine receptors.

Q. As of May 1987, would one of ordinary skill in the art have used the rabbit ear artery test for anti-Parkinsonian, to test for anti-Parkinsonian activity?

A. No.

Q. As of the date of this article, 1978, had the D2 receptor been classified?

A. No.

Q. Does this article change your opinion about whether one of ordinary skill in the art would have predicted in 1987 that ropinirole was centrally active based on its peripheral activity?

A. No.

Q. Why not?

A. Well, because there is nothing in this article that is to do with post-synaptic receptors in the brain, that could be used to predict an anti-Parkinsonian effect. There is no

Q. Are you familiar with the compound bromocriptine?

A. Yes.

Q. And do you recall Dr. Long's testimony about bromocriptine?

A. Yes, I do.

Q. What would one of ordinary skill in the art have known in May of 1987 about bromocriptine's interaction with dopamine receptors?

A. Bromocriptine was known to interact with both pre-synaptic and post-synaptic dopamine receptors in the peripheral and central nervous system.

Q. Would that knowledge have enabled one of ordinary skill at that time to predict that ropinirole hydrochloride would act at both peripheral and central and post-synaptic and pre-synaptic D2 receptors?

MR. DONOVAN: Objection. Leading.

THE COURT: Rephrase, please.

BY MS. WIGMORE:

Q. What if anything would one of ordinary skill in the art have concluded about ropinirole's activity at dopamine receptors based on this knowledge about bromocriptine as of May of 1987?

A. Well, I don't think one would have concluded anything, quite frankly, because ropinirole is an indolone compound, bromocriptine is a complex ergot derivative. And I think,

as we have heard, and certainly as Drs. Cannon and Long have talked, you cannot transpose information between one chemical class of dopamine agonists and another.

Q. Professor Jenner, do you still have PTX-117 before you?

A. You will have to tell me which number.

Q. That is Tab 5.

A. Thank you. That is the one I am looking at.

Q. If you could refer, please, to Page 1114. I want to direct your attention to the right-hand column, the last paragraph?

A. Okay.

Q. Could you read for us, please, the first three sentences of that paragraph?

A. "Costall and Naylor have noted that the literature has described numerous dopamine receptor subtypes based upon diverse techniques, behavioral, electrophysiological, biochemical, and others, using vertebrates and invertebrates. Evidence of classification is not always convincing, and correlation between the various subtypes is very difficult. Further, with terminologies ranging from DA-1, DA-2, D1, D2, DI, DE, AI, DA-alpha and DA-beta and even D-3, the literature seems to be impossibly confusing."

Q. Was that an accurate statement of the state of knowledge about dopamine receptors at that time?

Q. What compound is that?

A. 33 is the compound that we have been referring to as Compound 9.

Q. If you could refer, please, to the next page, Page 173. In the right-hand column, do you see the third paragraph, beginning, "I believe..."?

A. Yes, I do.

Q. Could you read that first sentence for us, please?

A. "I believe that the results of our 20 years of active study of dopamine permits us to make some conclusions. Probably many, if not most, of the dopaminergic agonist structure pharmacology correlations that have been made in the past (by us and by others) are naive and do not necessarily reflect the true nature of dopaminergic agonist receptor interactions, even though we can frequently use these correlations rationally to design biologically active compounds."

Q. And what would one of ordinary skill in the art have understood that to mean back in 1986?

A. One of ordinary skill in the art in that era would have been taught by this writing that it was not possible to make jumps between chemicals of different structural classes when trying to come to some conclusion about the structural requirements for activity at dopamine receptors.

Q. And are Compound 9 and ropinirole hydrochloride part

Q. And what series of compounds does this article address?

A. These compounds are what are called n,n-disubstituted dope means derivatives.

Q. Does dopamine hydrochloride fall within that chemical class?

A. It does not.

Q. And with respect to this article, what type of activity was found with respect to these dopamine derivatives?

A. The article suggests that these compounds had activity on both peripheral and central dopamine receptors.

Q. And would one of ordinary skill in the art have been able to conclude, in 1987, based on this article, that ropinirole would have activity at both the peripheral and central receptors?

MR. DONOVAN: Objection, leading.

MS. WIGMORE: I can rephrase, Your Honor.

THE COURT: Go ahead and rephrase. I'm not sure it was exactly leading but go ahead and rephrase.

BY MS. WIGMORE:

Q. Dr. Jenner, as of 1987, what, if anything, could one of ordinary skill have concluded from this article about the activity of ropinirole hydrochloride?

A. I think one of ordinary skill in the art would not

have been able to conclude anything because this is a paper dealing with n,n-disubstituted dopamine derivatives. It is not a paper dealing with indolone derivatives. And I think as we've now already established, you cannot make jumps from one class to another when considering these structure activity relationships.

Q. Professor Jenner, could you please turn to page 251 of this document?

A. (Witness complies.)

Q. And I want to refer you to the right-hand column, the third full paragraph beginning, "It is interesting."

A. Okay.

Q. Could you read that paragraph for us, please?

A. Yes. Okay.

"It is interesting to attempt some comparison between the actions of the symmetrically, n,n-disubstituted homologues of dopamine on peripheral and central mechanisms. First, it is tentatively suggested that the requirements for peripheral and central dopamine receptor stimulation may differ; for example, the ability to inhibit stimulation of the cardioaccelerator nerve decreased from methyl to propyl, whereas behavioral effects characteristic of cerebral dopamine receptor stimulation induced by peripheral drug administration decreased from propyl to methyl. Second, the present data give the first indication that the dopamine

receptors within the area postrema may differ from those within the periphery and other areas of the brain in their selectivity for only one homologue.

Q. Just for clarification, what is the area postrema?

A. The area postrema is an area of, I presume, the central nervous system which actually lies outside the blood brain area and is responsible for producing phenomena such as vomiting.

Q. Now, what would this paragraph have told one of ordinary skill in the art at the time about the relationship between peripheral and central dopamine receptors?

A. I think anyone of ordinary skill in the art at this time reading this paragraph would have come to the conclusion that peripheral and central dopamine receptors were different.

Q. And finally, Professor Jenner, do you agree that this article alone or in combination with other publications renders Claim 3 of the '860 patent obvious?

A. No.

Q. Why not?

A. I think that, for three reasons.

Firstly, there is no surety that peripheral dopamine receptors and central dopamine receptors are the same.

Secondly, there is no surety of penetration of

molecules through the blood brain barrier to exert an effect on the post-synaptic dopamine receptors as is required for Parkinson's disease.

And, thirdly, again, I think we clearly established that you cannot make a jump from one class of chemical compound to another when attempting to predict dopamine agonist activity.

Q. And you used the phrase "no surety" in the first two points. Could one of ordinary skill in the art have been able to reasonably predict, as of May of 1987, that ropinirole could treat Parkinson's disease?

A. In my opinion, there was no reasonable degree of predictability of effect in the art at this time.

MS. WIGMORE: Thank you, Professor Jenner. I have no further questions.

THE COURT: Mr. Donovan, your cross-examination.

CROSS-EXAMINATION

BY MR. DONOVAN:

Q. Good afternoon, Dr. Long. Excuse me.

THE COURT: I'm feeling that way, Mr. Donovan.

MR. DONOVAN: I spent a lot of time with Dr. Long yesterday and the day before. Good afternoon, Dr. Jenner.

A. The name is right, the time is wrong.

Q. Time flies. Dr. Jenner, in addition to being a